ABBOTT LABORATORIES
Global Pharmaceutical Regulatory Affairs

Douglas L. Sporn
Divisional Vice President
Global Pharmaceutical Regulatory Affairs
Telephone: (847) 937-7986
Facsimile: (847) 938-3346

200 Abbott Park Road
D-RA78, AP30-1
Abbott Park, Illinois 60064-6157
E-mail: doug.sporn@abbott.com

July 2, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0188 Request for Comments on the Draft Guidance on Development and Use of Risk Minimization Action Plans

Abbott Laboratories (Abbott) is pleased to have the opportunity to comment on the Draft Guidance on Development and Use of Risk Minimization Action Plans, published in the Federal Register on May 5, 2004.

In general, Abbott supports the Pharmaceutical Research and Manufacturers of America (PhRMA) responses sent to the FDA on this draft guidance and provides the additional attached comments.

Abbott wishes to acknowledge the Agency's foresight in addressing this very important issue in a multi-step process, e.g., a Concept Paper, public workshop, and Draft Guidance. This has afforded stakeholders the opportunity to provide well-considered and thorough input. It has also provided stakeholders a prospective view of the Agency's evolving thinking so that they can begin to consider system adjustments that will meet the needs of a robust risk management approach. We urge the Agency to consider a similar transparent and multi-step commentary process for other initiatives of like stature.

Should you have any questions, please contact Jill Sackett at (847)-937-4085 or by FAX at (847) 938-3346.

Sincerely,

Doug L. Sporn / jms

Douglas L. Sporn

2004D-0188 C7

Abbott

Abbott Comments on FDA Draft Guidance for Industry:
Development and Use of Risk Minimization Action Plans
Docket No. 2004D-0188

July 2, 2004

General Comments

Abbott Laboratories appreciates the opportunity to provide comments on this Draft Guidance. We are pleased to see the Agency's responsiveness to stakeholder concerns as reflected by some of the improvements made to this document in both content and clarification over the previously issued Concept Paper. In particular, we are reassured to see the Agency's improved emphasis that "routine" risk assessment and risk minimization are sufficient for most products. We are further encouraged to see risk discussed in a more balanced fashion with benefit, as both are inextricably linked.

However, there remain several areas of concern that deserve specific mention as discussed and tabulated below.

Abbott is pleased to see that the Risk Management Program "levels" have been eliminated, as such categorization would serve to unfairly stigmatize one product over another. The draft guidance, however, continues to divide the tools into three categories. This is likely to have a similar stigmatizing effect on products as the previously suggested numbered levels. Such categorization seems unnecessary from the view point of designing effective programs to minimize risk, especially since the guidance provides for selection of tools from more than one category as necessary to meet the perceived needs for a given product. The categories may have the effect of making sponsors reluctant to employ a tool from a "higher" category simply because of the perception that its inclusion would disadvantage the product in the marketplace. We recommend deleting the categories altogether from the description of available tools. Alternatively, if the categories are retained, an explanation to justify them should be provided.

There is improved acknowledgement of the potential burden of RiskMAPs on the health care delivery system. However, the document could be improved by addressing the steps that could be taken if a proposed RiskMAP is discouraged by the health care community or if an implemented RiskMAP program proves to be unfeasible for the health care community. Further, it should be recognized that the information available to assess such impact is anecdotal at best.

Abbott prefers the use of the term Risk Minimization Action Plan, or RiskMAP, instead of Risk Management Program, as the latter term more intuitively applies to both risk assessment *and* risk minimization activities. However, the Agency must be cognizant that even the term "RiskMAP" carries with it a negative distinction and could lead to misassumptions, including inappropriate product avoidance by the healthcare community and/or the lay public. We therefore urge the Agency to proceed cautiously with how the term RiskMAP is utilized.

We suggest that the term RiskMAP be used to facilitate regulatory communications between sponsors and the FDA, but that the Agency refrain from the using the term in

public disclosures, including redacted, post-approval packages. Disclosure of whether a company has a RiskMAP should be done at the discretion of the sponsor.

Currently the FDA selectively lists important information about certain products on its CDER web site under "Major Drug Information Pages." Products with well-publicized risk management programs are inconsistently designated. For example, Lotronex® has a "risk management program," while Thalomid™ has an "oversight program" and Oxycontin® describes a "Dear Healthcare Professional" letter. We ask the Agency to consider carefully the criteria it will use to post additional products with RiskMAPS in this section, and when such postings occur, that they do not designate the product as having a RiskMAP. Further, we request that the Agency re-examine its current "Major Drug Information Pages" content to remove references to whether or not a product has a "Risk Management Program."

In addition, the document remains unclear as to when a product will be deemed to have a RiskMAP. Today, many products utilize targeted education and outreach tools, including patient package inserts, CE programs, and DTC advertising but are not identified as having a Risk Management Program *per se*. In general, these are not necessarily targeted to minimize a specific risk but, instead, to improve overall familiarity with the product. We recommend including in the guidance some discussion of criteria that may be used to determine when such documents and programs would be considered to constitute a RiskMAP.

Specific Comments

Line(s)	Comment
171-173	The Agency asserts that a goal should reflect the "ideal outcome" of a RiskMAP. Ideals are rarely achieved. If goals are to be stated in this fashion, Section V., RiskMAP Evaluation, should include an acknowledgement that the acceptance criteria would target an outcome *less* than the stated goal. Otherwise, every evaluation is likely to indicate failure of the RiskMAP.
193	The Agency states in Footnote 6 that it "...recognizes that a generic product may have the same or similar benefit-risk balance as the innovator and may, therefore, be an appropriate candidate for consideration of a RiskMAP." We are hard-pressed to contemplate any instance in which a generic product would not require a RiskMAP that is equitable with that of its reference listed drug. 21 CFR 314.92 states that an ANDA product must meet the "same conditions of use" as the reference listed drug. The marketing of a product that is allowed to be substituted for an innovator product without a correspondingly robust RiskMAP raises serious safety concerns. As this type of change in "conditions of use" would not qualify for the suitability petition process described in 21 CFR 314.93(a), any generic sponsor seeking approval of a product with a less robust (or absent) RiskMAP should not qualify for the 505(j) approval route. Accordingly, this footnote should be revised to confirm an expectation that generic products are expected to conform to a RiskMAP equivalent to that for the reference listed drug.
222	Please clarify the statement "If factors are identified that can predict effectiveness..." Does this refer to effectiveness of the drug or of the RiskMAP tool(s)?

	or graphic matter. If these tools routinely accompany the product it would be helpful to remind sponsors that they are considered to be product labeling, and subject to the regulations pertaining to labeling.
284-285	Please clarify the qualified phrase "focused or limited promotional techniques such as product sampling or direct-to-consumer advertising." The two examples given are typically not "focused" or "limited" in light of how they are executed. Is the Agency suggesting a change in current practice for product sampling and DTC when conducted in the context of RiskMAPs?
501-503	It is pointed out that in some cases, pre-testing cannot be done. As an example, the guidance cites situations that demand rapid implementation post-marketing secondary to the emergence of newly recognized adverse events. There is no justification provided for the rapid implementation of an intervention of unknown value given the resources needed to implement a RiskMAP and the impact a RiskMAP may have on healthcare providers and patients. Perhaps, instead of emphasizing speed of implementation of a RiskMAP of unknown value in such cases, the guidance should emphasize the importance of selecting tools with a known track record as an initial response.
516-520	The limitations of spontaneous adverse event data are briefly outlined here. The Agency then recommends that systematic data collection in defined populations be conducted. Please clarify this recommendation. Is the Agency suggesting that sponsors conduct targeted analyses of their spontaneous event database or is it suggesting a prospective data collection outside of the spontaneous event reporting system? If it is the latter, significantly more detail is needed. It should be noted that systematic data collection has the disadvantage that it may not be representative of the larger patient population.
544-547	Privacy laws will severely restrict the ability to access, evaluate and reconcile death certificates with clinical trial subjects. Furthermore, in our experience, certain institutions refuse access to death certificates. We do not see this as being a viable suggestion and recommend that it be deleted.
642	This statement says that a sponsor "could" decide that a RiskMAP is warranted "...when marketing a generic product that references an innovator product with a RiskMAP." As mentioned in our comment on line 193, the requirement for a RiskMAP in such instances must not be discretionary. Furthermore, this statement suggests that the sponsor's decision could be made *after* the generic product has been launched. Inconsistent RiskMAP approaches for interchangeable products are clearly not in the interest of public health.
677	This section describes the contents of a RiskMAP submission. Guidance with regard to patent listing/certification should be included. We are aware of at least one instance in which a patented Risk Management Program has received Orange Book listing (reference NDA 20785 for Celgene's thalidomide capsules). Please clarify that "use" patents for RiskMAPs are eligible for Orange Book listing under current regulations. This guidance should include a reminder to provide any necessary patent listing and/or certification information.

ABBOTT LABORATORIES
Global Pharmaceutical Regulatory Affairs

Douglas L. Sporn
Divisional Vice President
Global Pharmaceutical Regulatory Affairs
Telephone: (847) 937-7986
Facsimile: (847) 938-3346

200 Abbott Park Road
D-RA78, AP30-1
Abbott Park, Illinois 60064-6157
E-mail: doug.sporn@abbott.com

July 2, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0188 Request for Comments on the Draft Guidance on Development and Use of Risk Minimization Action Plans

Abbott Laboratories (Abbott) is pleased to have the opportunity to comment on the Draft Guidance on Development and Use of Risk Minimization Action Plans, published in the Federal Register on May 5, 2004.

In general, Abbott supports the Pharmaceutical Research and Manufacturers of America (PhRMA) responses sent to the FDA on this draft guidance and provides the additional attached comments.

Abbott wishes to acknowledge the Agency's foresight in addressing this very important issue in a multi-step process, e.g., a Concept Paper, public workshop, and Draft Guidance. This has afforded stakeholders the opportunity to provide well-considered and thorough input. It has also provided stakeholders a prospective view of the Agency's evolving thinking so that they can begin to consider system adjustments that will meet the needs of a robust risk management approach. We urge the Agency to consider a similar transparent and multi-step commentary process for other initiatives of like stature.

Should you have any questions, please contact Jill Sackett at (847)-937-4085 or by FAX at (847) 938-3346.

Sincerely,

Doug L. Sporn / jms

Douglas L. Sporn

Abbott

Abbott Comments on FDA Draft Guidance for Industry:
Development and Use of Risk Minimization Action Plans
Docket No. 2004D-0188

July 2, 2004

General Comments

Abbott Laboratories appreciates the opportunity to provide comments on this Draft Guidance. We are pleased to see the Agency's responsiveness to stakeholder concerns as reflected by some of the improvements made to this document in both content and clarification over the previously issued Concept Paper. In particular, we are reassured to see the Agency's improved emphasis that "routine" risk assessment and risk minimization are sufficient for most products. We are further encouraged to see risk discussed in a more balanced fashion with benefit, as both are inextricably linked.

However, there remain several areas of concern that deserve specific mention as discussed and tabulated below.

Abbott is pleased to see that the Risk Management Program "levels" have been eliminated, as such categorization would serve to unfairly stigmatize one product over another. The draft guidance, however, continues to divide the tools into three categories. This is likely to have a similar stigmatizing effect on products as the previously suggested numbered levels. Such categorization seems unnecessary from the view point of designing effective programs to minimize risk, especially since the guidance provides for selection of tools from more than one category as necessary to meet the perceived needs for a given product. The categories may have the effect of making sponsors reluctant to employ a tool from a "higher" category simply because of the perception that its inclusion would disadvantage the product in the marketplace. We recommend deleting the categories altogether from the description of available tools. Alternatively, if the categories are retained, an explanation to justify them should be provided.

There is improved acknowledgement of the potential burden of RiskMAPs on the health care delivery system. However, the document could be improved by addressing the steps that could be taken if a proposed RiskMAP is discouraged by the health care community or if an implemented RiskMAP program proves to be unfeasible for the health care community. Further, it should be recognized that the information available to assess such impact is anecdotal at best.

Abbott prefers the use of the term Risk Minimization Action Plan, or RiskMAP, instead of Risk Management Program, as the latter term more intuitively applies to both risk assessment *and* risk minimization activities. However, the Agency must be cognizant that even the term "RiskMAP" carries with it a negative distinction and could lead to misassumptions, including inappropriate product avoidance by the healthcare community and/or the lay public. We therefore urge the Agency to proceed cautiously with how the term RiskMAP is utilized.

We suggest that the term RiskMAP be used to facilitate regulatory communications between sponsors and the FDA, but that the Agency refrain from the using the term in

public disclosures, including redacted, post-approval packages. Disclosure of whether a company has a RiskMAP should be done at the discretion of the sponsor.

Currently the FDA selectively lists important information about certain products on its CDER web site under "Major Drug Information Pages." Products with well-publicized risk management programs are inconsistently designated. For example, Lotronex® has a "risk management program," while Thalomid™ has an "oversight program" and Oxycontin® describes a "Dear Healthcare Professional" letter. We ask the Agency to consider carefully the criteria it will use to post additional products with RiskMAPS in this section, and when such postings occur, that they do not designate the product as having a RiskMAP. Further, we request that the Agency re-examine its current "Major Drug Information Pages" content to remove references to whether or not a product has a "Risk Management Program."

In addition, the document remains unclear as to when a product will be deemed to have a RiskMAP. Today, many products utilize targeted education and outreach tools, including patient package inserts, CE programs, and DTC advertising but are not identified as having a Risk Management Program *per se*. In general, these are not necessarily targeted to minimize a specific risk but, instead, to improve overall familiarity with the product. We recommend including in the guidance some discussion of criteria that may be used to determine when such documents and programs would be considered to constitute a RiskMAP.

Specific Comments

Line(s)	Comment
171-173	The Agency asserts that a goal should reflect the "ideal outcome" of a RiskMAP. Ideals are rarely achieved. If goals are to be stated in this fashion, Section V., RiskMAP Evaluation, should include an acknowledgement that the acceptance criteria would target an outcome *less* than the stated goal. Otherwise, every evaluation is likely to indicate failure of the RiskMAP.
193	The Agency states in Footnote 6 that it "...recognizes that a generic product may have the same or similar benefit-risk balance as the innovator and may, therefore, be an appropriate candidate for consideration of a RiskMAP." We are hard-pressed to contemplate any instance in which a generic product would not require a RiskMAP that is equitable with that of its reference listed drug. 21 CFR 314.92 states that an ANDA product must meet the "same conditions of use" as the reference listed drug. The marketing of a product that is allowed to be substituted for an innovator product without a correspondingly robust RiskMAP raises serious safety concerns. As this type of change in "conditions of use" would not qualify for the suitability petition process described in 21 CFR 314.93(a), any generic sponsor seeking approval of a product with a less robust (or absent) RiskMAP should not qualify for the 505(j) approval route. Accordingly, this footnote should be revised to confirm an expectation that generic products are expected to conform to a RiskMAP equivalent to that for the reference listed drug.
222	Please clarify the statement "If factors are identified that can predict effectiveness..." Does this refer to effectiveness of the drug or of the RiskMAP tool(s)?

	or graphic matter. If these tools routinely accompany the product it would be helpful to remind sponsors that they are considered to be product labeling, and subject to the regulations pertaining to labeling.
284-285	Please clarify the qualified phrase "focused or limited promotional techniques such as product sampling or direct-to-consumer advertising." The two examples given are typically not "focused" or "limited" in light of how they are executed. Is the Agency suggesting a change in current practice for product sampling and DTC when conducted in the context of RiskMAPs?
501-503	It is pointed out that in some cases, pre-testing cannot be done. As an example, the guidance cites situations that demand rapid implementation post-marketing secondary to the emergence of newly recognized adverse events. There is no justification provided for the rapid implementation of an intervention of unknown value given the resources needed to implement a RiskMAP and the impact a RiskMAP may have on healthcare providers and patients. Perhaps, instead of emphasizing speed of implementation of a RiskMAP of unknown value in such cases, the guidance should emphasize the importance of selecting tools with a known track record as an initial response.
516-520	The limitations of spontaneous adverse event data are briefly outlined here. The Agency then recommends that systematic data collection in defined populations be conducted. Please clarify this recommendation. Is the Agency suggesting that sponsors conduct targeted analyses of their spontaneous event database or is it suggesting a prospective data collection outside of the spontaneous event reporting system? If it is the latter, significantly more detail is needed. It should be noted that systematic data collection has the disadvantage that it may not be representative of the larger patient population.
544-547	Privacy laws will severely restrict the ability to access, evaluate and reconcile death certificates with clinical trial subjects. Furthermore, in our experience, certain institutions refuse access to death certificates. We do not see this as being a viable suggestion and recommend that it be deleted.
642	This statement says that a sponsor "could" decide that a RiskMAP is warranted "...when marketing a generic product that references an innovator product with a RiskMAP." As mentioned in our comment on line 193, the requirement for a RiskMAP in such instances must not be discretionary. Furthermore, this statement suggests that the sponsor's decision could be made *after* the generic product has been launched. Inconsistent RiskMAP approaches for interchangeable products are clearly not in the interest of public health.
677	This section describes the contents of a RiskMAP submission. Guidance with regard to patent listing/certification should be included. We are aware of at least one instance in which a patented Risk Management Program has received Orange Book listing (reference NDA 20785 for Celgene's thalidomide capsules). Please clarify that "use" patents for RiskMAPs are eligible for Orange Book listing under current regulations. This guidance should include a reminder to provide any necessary patent listing and/or certification information.